New Vaccine Safety Surveillance Updates

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Outline of Topics

- Tdap formulations-Adacel® and Boostrix®
  - Boostrix licensed for adolescents aged 10-18 years
- Zoster vaccine-Zostavax®
- Data sources-
  - Vaccine Adverse Event Reporting System (VAERS)
  - Vaccine Safety Datalink (VSD)
  - Tdap safety evaluation during mass vaccination of healthcare personnel

VAERS Background/Update

- National passive surveillance system for U.S. licensed vaccines; jointly operated with FDA
- Subject to underreporting, temporal and other reporting biases, general inability to assess causality for individual reports
- Since January 17 2007, adverse events coded using Medical Dictionary for Regulatory Activities (MedDRA); this is considered the international standard

VSD Background/Update

- Automated large linked database involving eight geographically diverse managed care organizations (MCOs)
- Covers approximately 3% of U.S. population
- Recently implemented “rapid cycle” analysis (RCA) for newly licensed vaccines
- May be underpowered to detect very rare adverse events

Safety Data for Tdap: Events Reported to VAERS

- 1379 total reports received as of January 29, 2007
  - Demographics
    - 67% Females (n=928)
    - 2% Unknown (n=21)
    - 43% (n=592) involve persons 11-18 years old

Vaccine	N	%
Adacel	1092	80
Boostrix	268	20

*excludes foreign reports

Adverse Events Reported to VAERS

- Onset
  - 31% (n=434) reports on the day of vaccination (i.e. day 0)
  - 33% (n=455) reports on day 1
- Recovery
  - 88% with known status recovered at time report submitted
- Source of reports
  - 53% (n=714) provider
  - 8% (n=106) vaccine manufacturer
  - 6% (n=81) patient/parent

Most Frequently Reported Symptoms (% of reports)

Pyrexia (fever)	n = 345 (25.4)
Pain	n = 263 (19.3)
Injection site erythema	n = 260 (19.1)
Injection site pain	n = 227 (16.7)
Headache	n = 175 (12.9)

- As coded using the MedDRA preferred terms.
- More than one code may be assigned to a single event.

Serious Reports*

- 71 serious reports (5% of total reports)
  - Tdap given alone in 34 reports
- 3 death reports
- 52 required hospitalization

Adacel	53
Boostrix	17

* Defined by Code of Federal Regulations as involving hospitalization, death, disability, life threatening illness, or certain other medically important conditions

Death Reports

Total = 3

- 13 y/o male received Tdap; 14 days later died suddenly of cardiac arrhythmia while walking. History of rash following cephalosporin and reactive airway disease. Coroner reported cause of death as cardiac arrhythmia due to undetermined cause.
- 62 y/o male received Tdap, Hep A, Yellow Fever, Typhoid and IPV; 10 days later died of a myocardial infarction due to atherosclerotic disease. History of hyperlipidemia. Autopsy was not performed.
- 52 y/o male received Tdap; 1 day later died of cardiac arrest due to pulmonary edema. Autopsy was not performed.

Guillain Barré Syndrome (GBS)

- 8 total cases
  - 7/8 reports >18 y/o
  - 5/8 occurred in males
  - Onset
    - 4 reports day 0-2
    - 1 report day 10-14
    - 1 report day 15-30
    - 2 reports day 31-60
  - 3 patients recovered; other 5 undergoing rehabilitation or outpatient therapy

Vaccine(s)	N
Tdap	4
Tdap, MCV4, HepB	1
Tdap, Flu, HepA/B	1
Tdap, Flumist, HepA/B, IPV, Menomune, MMR	1
Tdap, Flumist HepA/B, Yellow Fever, IPV	1

Tdap Administration Errors

- 56 total reports
  - 16 reports Tdap given instead of DTaP
  - 5 reports Tdap given instead of Pediarix (DTaP, IPV, Hep B)
  - 6 reports of Tdap given to patients older than 65
    - Also 6 reports of receipt of DTaP (Daptacel) instead of Adacel; only one minor local adverse reaction
  - 1 instance of patient with hx of pertussis vaccine allergy given Tdap; prophylactic treatment given and no adverse event occurred.

Observational Assessment of Tdap Safety in an Outbreak Setting, 2006

- **Outbreak of suspected pertussis at a major medical center**
- **Tdap offered to all healthcare personnel (HCP), including persons vaccinated with tetanus and diphtheria toxoids (Td) or tetanus toxoid (TT) <2 years earlier**
  - **4524 (72% of HCP) vaccinated**

Methods

- **Surveyed vaccinees about adverse events (AEs) during 2 weeks after vaccination to assess**
  - **Solicited AEs**
    - **Pain at injection site***
    - **Redness at injection site***
    - **Swelling at injection site***
    - **Fever (subjective)**
  - **Medical visits**
  - **Unsolicited AEs**
- **Enhanced surveillance for serious adverse events (SAEs) for 2 months after vaccination**

* Moderate and severe categories; definitions adapted from Tdap prelicensure trials

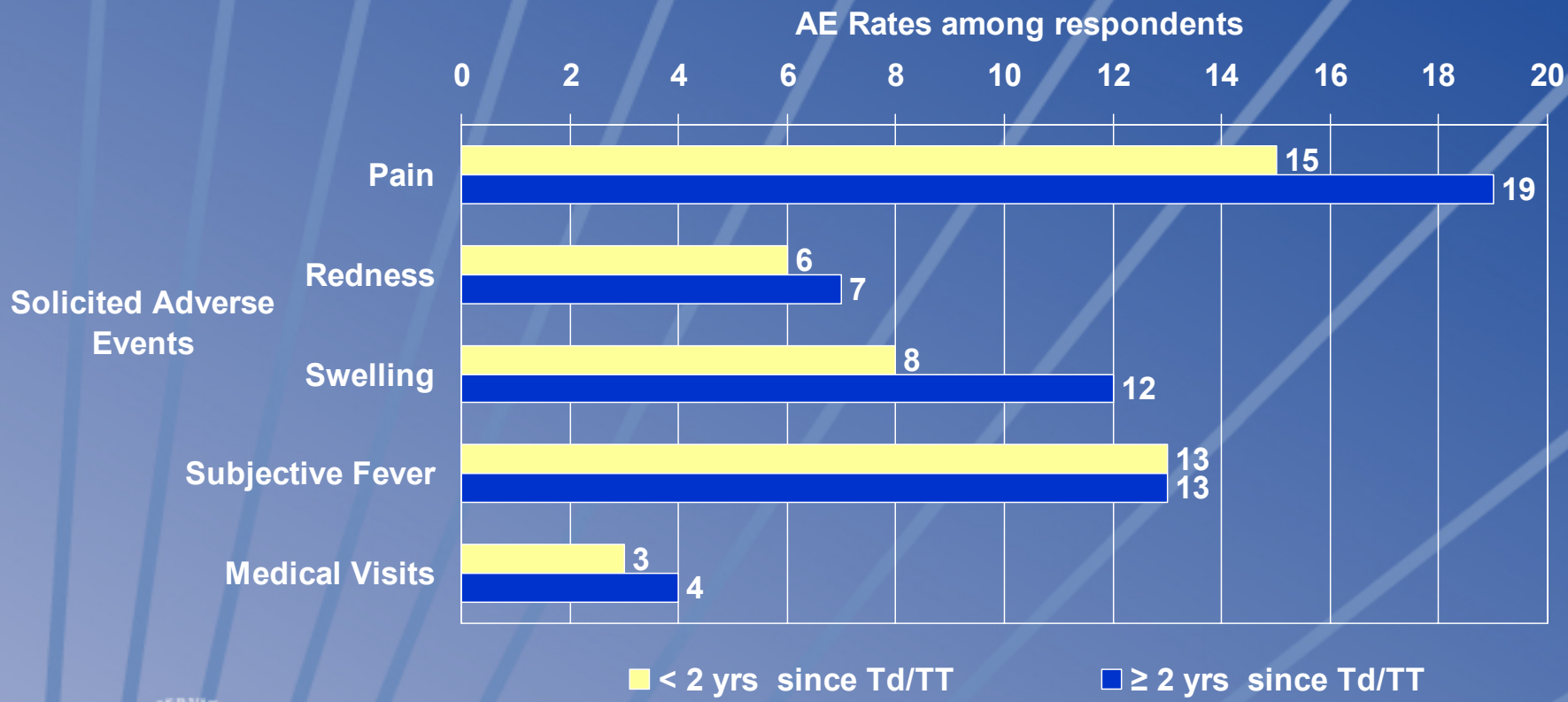
Survey Response and Overall AE Rates

- 59% response rate (2676/4524)
- Responders
  - 79% female
  - Median age: 46 years (16-83 years)
  - Demographically similar to HCP population
- Overall rates of solicited AEs among responders:

Pain*	18%
Redness*	7%
Swelling*	11%
Fever (subjective)	13%
Medical Visits	5%

* Moderate + severe

AE Rates by Interval since prior Td/TT



Upper 95% confidence limit on Δ <10% for all comparisons, where Δ is the difference in rates (<2 years minus ≥2 years)

Persons > 64 y/o, pregnant women excluded

Summary: Tdap Post-Licensure Safety

- Most events reported to VAERS:
  - Were non-serious (95%) and had onset 0-1 days after vaccination (64%)
  - Involved local and systemic symptoms consistent with known safety profile
- Among serious events reported to VAERS:
  - Deaths not consistent with causal relationship to vaccine
  - GBS reports were not clustered by plausible onset interval or single vaccine exposure

Summary: Tdap Post-Licensure Safety (cont)

- Among HCP receiving Tdap in an apparent outbreak setting, preliminary analysis identified:
  - No increased risk for adverse reactions among those more recently vaccinated with Td/TT (< 2 yrs)
  - Rates of local reactions were consistent with adult Tdap pre-licensure data

Adverse Events after Zostavax® [Zoster Vaccine, Live (Oka/Merck)] reported to VAERS through 01/15/07

Net doses distributed through January 2007 = ~365,000

Total reports = 194

- 185 (95%) Nonserious
- 9 (5%) Nonfatal Serious
- 0 Deaths

Adverse events after Zostavax® reported to VAERS through 01/15/07

Demographics (N=194)

Median age: 65 years

Gender:

Male:	47	(24%)
Female:	138	(71%)
Unknown:	9	(5%)

Median interval from vaccination-onset of symptoms: 1 day

Adverse events after Zostavax® reported to VAERS through 01/15/07 (N=194)

Event	No.	%
Injection site reaction*	49	25.3
Herpes zoster-like rash	41	21.1
Rash (other than herpes zoster, varicella, urticaria or injection site rash)	35	18.0
Pruritus	32	16.5
Fever	15	7.7
Medication error	13	6.7
HA	13	6.7
Urticaria	9	4.6
Myalgia	4	2.1
CVA	3	1.5
Flu-like illness	3	1.5
Vertigo	3	1.5

Adverse event reports after Zostavax®, VAERS through 01/15/07

Rashes:

Herpes zoster-like (n=41)

Median age: 68 yrs
Males: 11 Females: 29 unknown: 1
Median days to onset: 4 days

Varicella = 0

Rashes other than herpes zoster- like or injection site or urticaria (n=35)

Median age: 66.5 yrs
Males: 12 Females: 23
Median days to onset: 3 days

“Medical error” reports after Zostavax®, VAERS through 01/15/07

- 14 month old male received Zostavax on 7.26.06 instead of Varicella virus vaccine. 3 days later he developed “pocks” and “red spots;” sx. resolved.
- I y.o. female received Zostavax instead of Proquad.
- 4 y.o. female received Zostavax instead of Proquad.
- 4 y.o. received Zostavax instead of Varicella, I day later developed inj site rx, 7 days later fever, HA, 9 days later chickenpox.
- 1 y.o. female received Zostavax instead of Varicella. 1 week later developed fever, HA.

- Adult received Varicella vaccine instead of Zostavax.
- 60 y.o. vaccinated with Zostavax instead of Varicella to prevent chickenpox.

VSD Project: Surveillance for adverse events following zoster vaccine

Vaccination and medical records from all settings: Inpatient, Outpatient, and Emergency Department

Number of persons 50+ years of age as of Dec. 2004:

Managed Care Organization (MCO)	No. Enrolled
Kaiser Permanente, Northern California	954,821
Kaiser Permanente, North West	134,800
Group Health Cooperative, Seattle, WA	134,673
	1,224,294

VSD Surveillance: zoster vaccine safety

Rationale for surveillance of specific adverse events:

- **Commonly reported in VAERS following zoster vaccine**
- **Known serious sequelae of varicella zoster virus infection or herpes zoster**
- **Medical conditions causing serious morbidity or mortality in adults 60+ years old.**
- **Adverse events known to follow other vaccines**

Surveillance for adverse events following zoster vaccine

Adverse Events List

- Arthus reaction
- Aseptic meningitis
- Bell's Palsy
- Cerebellar Ataxia
- Cervical Myelopathy
- Congestive Heart Failure
- Dilated Cardiomyopathy
- Disseminated Zoster, Varicella
- Encephalitis
- Encephalopathy
- Herpes Zoster
- Myocardial Ischemia
- Myo/pericarditis
- Polymyalgia rheumatica
- Ramsay-Hunt syndrome
- Stroke; TIA
- Thrombocytopenia/ITP

VSD Surveillance: zoster vaccine safety

Important features of safety data analysis plan:

- **Safety data will be examined monthly using sequential monitoring with separate stopping boundaries for each AE.**

- **Presence of some underlying medical conditions may affect likelihood of vaccination. Case-series methodology will be used to adjust for each subject's baseline risk of AE.**
  - **Stratified Cox proportional hazards model with interim monitoring**

Summary: Zoster vaccine post-licensure safety

- Most events reported to VAERS expected on the basis of pre-licensure study, safety monitoring plan, and age of target population
  - Very small number of SAE
  - Most reported rashes, whether zosteriform or not, occurred within 4 days after vaccination
  - Administration errors have occurred in adults and children
- Sequential safety monitoring among a cohort of 660,000 persons ≥ 60 is being undertaken within VSD

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SAE in Total Vaccinated Cohort

- 3 total serious adverse events
- Case 1: 41 y/o female with anaphylaxis 6 days after vaccination
  - History of other anaphylactic reactions to uncertain allergens
- Case 2: 37 y/o male with GBS
  - Onset 11 days after Tdap
  - EEG and MRI findings consistent
  - Patient not hospitalized; full recovery
- Case 3: 40 y/o female with biopsy confirmed eosinophilic nephritis
  - Kidney transplant patient before Tdap